Symposium overview: Fructose in Physiology

Author: Javier T. Gonzalez
Affiliation: Department for Health, University of Bath, Bath, UK.
Email: J.T.Gonzalez@bath.ac.uk

One of the first uses of the term “fructose” was in 1857 by William Allen Miller FRS, and it was already known then that fructose was a distinctive carbohydrate, characterised by sweet taste (Miller, 1957). In most circumstances dietary free sugars can also be classified as fructose-containing carbohydrates (e.g. sucrose, high-fructose corn syrup), and the fructose component of these sugars is thought to be primarily responsible for unique metabolic effects. The role of sugars in the diet could be viewed as contentious, with many arguing that dietary sugar is the cause of type 2 diabetes and obesity (Bray & Popkin, 2014), whereas others posit that dietary sugars are innocuous to healthy individuals (Archer, 2018). One reason for this confusion and conflict is that much evidence presented is observational and/or based upon self-report assessments of dietary intake or physical activity. This is a problem, because observational data can never definitely establish cause-and-effect and can lead to spurious, misleading correlations. Furthermore, self-report methods are subject to observation and reporting biases. Herein lies the potential for a physiological approach to solve some of this confusion and conflict.

By understanding mechanistic links, we can explain some apparent discrepancies in observational data, and also take a step towards establishing causality. Plausible physiological links can increase confidence in causality of a behaviour when randomized controlled trials with hard endpoints would be considered unethical or impossible to perform. For example, it might be deemed unethical to randomise people to high *versus* low fructose intakes for decades to establish whether fructose intake causes type 2 diabetes or cardiovascular disease. However, by assessing the effects of fructose intake of physiological process that underlie disease risk, shorter-term studies can be used to establish causal effects of fructose intake, without necessarily affecting long-term health risk.

“Fructose in Physiology: Friend or Foe” was the title of a Symposium delivered at Europhysiology 2018 in London (UK), and was supported by *The Journal of Physiology*. The aim of this symposium was to bring together leading researchers across various career stages to discuss the physiology of fructose metabolism in

health and disease. In doing so, this symposium highlighted the potential mechanisms by which fructose may exert metabolic effects within specific populations, thereby overcoming some of the confusion around fructose and health.

Pinnick and Hodson (2019) describe the potential tissue- and sex-specific effects of fructose metabolism. Short-term (<7 days) high-fructose intake can increase plasma triglyceride concentrations and intrahepatic fat content, which are implicated in metabolic disease risk (Pinnick & Hodson, 2019). The mechanisms by which high fructose intake increases plasma triglyceride concentrations includes hepatic *de novo* lipogenesis (*DNL*) and fatty acid oxidation (Pinnick & Hodson, 2019). A novel focus was the discussion of the potential effects of fructose on adipose tissue metabolism, which could be direct or indirect (Pinnick & Hodson, 2019). The classical view is that the splanchnic tissues are the primary site of fructose metabolism (Gonzalez & Betts, 2018), and therefore adipose tissue is unlikely to be directly affected by fructose intake. Nevertheless, fructose could indirectly affect adipose tissue metabolism *via* increased plasma lactate concentrations following fructose consumption (Liu *et al.*, 2009; Gonzalez *et al.*, 2015). Furthermore, there is potential for some direct effects of fructose on adipose tissue, since it has been recently estimated that ~15% of a 30-g oral fructose load can escape first-pass splanchnic metabolism and thereby be exposed to peripheral tissues (Francey *et al.*, 2019). In addition to evidence that adipose tissue expresses the fructose-specific transporter, GLUT5, it is plausible that fructose could have some direct effects on adipose tissue, and this will be an important avenue for future research (Pinnick & Hodson, 2019). With respect to sex-specific responses, there is some evidence that males may display greater metabolic perturbations to high fructose intake when compared to females, including increased incorporation of fructose carbons into very low-density lipoprotein (VLDL)-TAG palmitate (reflective of hepatic *DNL*), greater suppression of fat oxidation, and increased basal endogenous glucose production (Pinnick & Hodson, 2019). However, other work has shown that females displayed higher hepatic *DNL* than males, when assessed using deuterium oxide (Low *et al.*, 2018). The discrepancies between studies may be explained by doses of fructose ingested (absolute vs normalised to fat-free mass), the method of assessing hepatic *DNL*, or participant characteristics and background diet. Accordingly, fructose can clearly stimulate lipogenesis in hepatocytes, but there is a need to further understand the sex-specific effects of fructose intake on metabolism and health.

Von Holstein-Rathlou and Gillum (2019) discuss a key potential regulator of fructose intake, fibroblast growth factor 21 (FGF21). FGF21 is a hepatically-derived hormone that, in mice, can be produced in response to low-protein and ketogenic diets, fructose feeding and ethanol (von Holstein-Rathlou & Gillum, 2019). It has also been shown that FGF21 preferentially inhibits *ad libitum* consumption of sugars and ethanol in mice, without affecting the intake of other dietary nutrients such as non-sugar carbohydrates, fat and protein, thereby exerting negative-feedback (von Holstein-Rathlou & Gillum, 2019). In humans, ingestion of sugars and ethanol can also stimulate FGF21 secretion, and genetic variants in the FGF locus have been associated with reported intakes of sweet foods (Søberg *et al.*, 2017). The potential mechanisms by which FGF21 is thought to regulate feeding behaviours is thought to involve the activation of the FGF21 receptor complex (comprising FGF receptor 1c and beta-klotho) in the paraventricular nucleus of the hypothalamus (von Holstein-Rathlou & Gillum, 2019). This opens up the intriguing possibility of reducing free-living sugar (and ethanol) intakes by treatment with FGF21 or by making use of other strategies that can increase endogenous FGF21 production.

Fuchs et al. (2019) describe how athletes can exploit some of the metabolic effects of fructose to benefit endurance performance and recovery. Intestinal fructose absorption primarily occurs via GLUT5. This contrasts with glucose, which is primarily absorbed via the sodium-dependent glucose transporter, SGLT1 (Fuchs *et al.*, 2019). Since SGLT1 is thought to be saturable at a rate of 1 g/min this can limit the amount of exogenous carbohydrate that athletes can ingest and metabolise during exercise. However, by combining fructose with glucose it is possible to make use of both of these intestinal transport pathways and thereby deliver more exogenous carbohydrate to the circulation, whilst also decreasing gastrointestinal discomfort associated with ingestion of large amounts of carbohydrate during exercise (Gonzalez *et al.*, 2015; Fuchs *et al.*, 2019). A higher availability of carbohydrates during exercise can have performance benefits in many endurance sports, thereby highlighting a potential beneficial role of fructose-containing carbohydrates. Furthermore, rapid restoration of depleted glycogen stores is a key factor dictating recovery time in multi-stage endurance events. Since fructose can potently stimulate hepatic glycogen synthesis (Fuchs *et al.*, 2016) there is potential for fructose-containing carbohydrates to accelerate recovery. Indeed, when the total amount of carbohydrate is matched, the ingestion of fructose-glucose mixtures can double the rate of liver glycogen repletion

in recovery from exercise, when compared to glucose-based carbohydrates (Fuchs *et al.*, 2019). Furthermore, ingestion of fructose-containing carbohydrates during recovery from exercise can enhance subsequent endurance running capacity, when compared to glucose-based carbohydrates (Maunder *et al.*, 2018). Therefore, at least for specific scenarios, fructose-containing carbohydrate can be useful for athletic performance.

Whilst fructose ingestion may provide a benefit to certain athletic events, a reasonable question to ask is whether such fructose intake is detrimental to the health of athletes. Tappy and Rosset (2019) describe the potential for physical activity to protect against the negative metabolic effects of high-fructose intake, independent from total energy balance (i.e. when controlling for negative energy balance induced by exercise). Whilst high-fructose intake can increase hepatic DNL, intrahepatic fat content, hepatic insulin resistance and plasma triglyceride concentrations in sedentary individuals, all these responses can be prevented under conditions of high physical activity (Tappy & Rosset, 2019). Fructose ingested during conditions of high energy output is thought to be directed more to lactate and glucose for utilisation as a fuel by skeletal muscle, and less to triglycerides *via DNL*. The authors therefore speculate that the negative metabolic health consequences of high-fructose intake occur when fructose intake exceeds the capacity of the liver to release lactate and glucose for skeletal muscle to utilise (Tappy & Rosset, 2019). This may be more likely to occur under conditions of low energy output, where skeletal muscle utilisation of circulating glucose and lactate is low. The authors propose that this could contribute to regulating hepatic fructose metabolism *via* a feedback mechanism that is yet to be definitely established.

Hengist et al. (2019) discuss a further potential mechanism that could explain the protection against fructose-induced metabolic impairments conferred by high levels of physical activity. Hepatic glycogen content plays a key role in regulating hepatic lipid metabolism by acting on both *DNL* and on hepatic fatty acid oxidation (Hengist *et al.*, 2019). Hengist et al. (2019) discuss the evidence that suggests "pushing" glucose into the liver and saturating liver glycogen concentrations increases *DNL* and hypertriglyceridaemia, whereas increasing the inherent capacity for liver glycogen storage does not detrimentally alter plasma triglyceride concentrations. This is consistent with the notion that net lipid synthesis is exacerbated when glycogen stores are saturated. Therefore, under conditions where hepatic glycogen stores are

low, or are undergoing an increased rate of turnover, there is likely to be lower rates of hepatic *DNL* and increased rates of hepatic fatty acid oxidation. The net result is less lipid synthesis. Furthermore, this may contribute to the mechanisms explaining why fructose can stimulate lipid synthesis to a greater extent than glucose, since fructose potently stimulates hepatic glycogen synthesis at rest and post-exercise (Petersen *et al.*, 2001; Fuchs *et al.*, 2016). Hepatic glycogen status may thereby provide a key link between the energy status of an individual and the metabolic responses to fructose intake.

In summary, this collection of review articles illuminates several key aspects of fructose metabolism. It is clear that excessive fructose intakes in sedentary individuals can induce a number of metabolic effects that may be detrimental to health. Whether males or females are more sensitive to the effects of fructose intake remains to be established. The hormone FGF21 could hold promise in reducing the levels of fructose intake when a high-fructose intake is undesirable and could therefore contribute to improvements in metabolic health. The metabolic effects of fructose ingestion can be utilised to benefit endurance performance and recovery in athletes, and these athletes seem to be protected against the negative metabolic effects of high-fructose intake. The mechanisms underlying exercise-induced protection against these metabolic effects remains to be established but may involve the greater conversion of fructose into glucose and lactate for oxidation rather than conversion into lipid, and these processes could be regulated by hepatic glycogen content. These physiological mechanisms provide a better understanding of why specific populations seem to be more or less vulnerable to high-fructose intakes and can be targeted for improving metabolic health.

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